Review Article

Stem Cell INVESTIGATION

Literature review of cancer stem cells in oral lichen planus: a premalignant lesion

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Objective: As there is no review study about cancer stem cells (CSCs) involved in the pathogenesis of oral lichen planus (OLP), for the first time we review the role of these cells in OLP and this hypothesis may be a clue for the evaluation of the premalignancy of OLP.

Background: Cellular mediated immune responses are the main etiopathogenesis in OLP and it is a potentially premalignant lesion. One of the factors proposed in the pathogenesis of OLP and the comparable trend of this autoimmune disease to squamous cell carcinoma (SCC) are CSCs. CSCs have been detected in several solid tumors including head and neck cancers, and have special characteristics including metastasis and resistance to chemotherapy.

Methods: Related keywords were searched and risk of bias assessment was done for each study.

Conclusions: Among all of the studies reviewed in this article, all markers had increased expression in OLP compared to controls that are consistent with SCC. Only CD44 was in contradiction to other papers, in which different expression of CD44 strains was measured in different samples such as saliva and tissue. Based on the results of this review and more studies in the future by investigating the levels of these markers in OLP, it may be possible to determine the prognosis and course of the disease for each patient individually.

Keywords: Cancer stem cell (CSC); malignancy; oral lichen planus (OLP)

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Background

Oral lichen planus (OLP) is a common chronic mucous dermal immunological inflammatory disorder, with unknown etiology (1,2). Recent data propose cellular mediated immune responses as the main etiopathogenesis (3). In contrast, lichenoid reactions are lesions that have a detectable etiology, but they may be very similar to Lichen Planus clinically and histologically, and as such differentiation may be difficult (2). OLP is twice as more prevalent among women than among men, and its average age is 55 years old, though it has also been reported among children and adolescents (1). Clinically, OLP appears in six forms: papular, reticular, plaque-like, atrophic (erythematous), erosive, and bullous, with erosive and bullous forms having the potential to change into an ulcer (1). The main symptoms resulting from the erosive, atrophic, and bullous forms whether in OLP or lichenoid lesions include pain, burning sensation, and bleeding (2,3). The set of these symptoms can adversely affect the quality of life of the patients. The prevalence of malignant changes in OLP has been reported to be 0–10%. Irrespective of the prevalence of malignant changes,

WHO has classified OLP as a potentially premalignant lesion. Its maximum prevalence is considered in erosive and ulcerative types (4).

One of the factors proposed in the pathogenesis of OLP and the comparable trend of this autoimmune disease to squamous cell carcinoma (SCC) are cancer stem cells (CSCs).

CSCs are considered a small subset of cells, which are capable of developing a group of tumors and originating from a limited number of cells (5-7). Cells should have regenerative properties *in vivo*, which are specifically observed in the re-growth of undetectable and heterogeneous tumors after the transfer of CSCs in secondary and tertiary receptors (5). Eventually, these cells should potential for differentiation, to develop a copy of the main tumor from undifferentiated cells. There are two hypotheses for the origin of CSCs (7): (I) origin comes from somatic tissue cells, which undergo genetic mutations, become cancerous, and acquire stem properties; (II) it comes from embryonic stems or adult cells in response to genetic mutations. Its onset could be dependent on the site of the tumor origin. The theory for the development of head and neck cancer can be summarized as follows:

Through the aggregation of genetic changes during acute inflammations through large consumption of tobacco and alcohol, mechanical stimulations, or viral infection, spontaneous aggregation of different genetic changes, which result in malignant manifestations. The clonal divergence and selection lead to the formation of a carcinoma (6,7).

In previous studies, it was shown that CSCs consist of CD44, ALDH, CD133, CD24 are involved in the development of oral SCC (5,7). In various papers, it has been shown that CD44 is involved in the progress of tumor and tumor metastasis through regulating growth, survival, differentiation, and migration (5). CD44 is a biomarker, involved in colon, breast, prostate, and pancreas tumors (7). Gene expression analysis has indicated a possible functional role for BMI-1 in head and neck cancer, which is differently expressed in head and neck cancer cells containing CD44, in comparison with tumor cells lacking CD44. BMI-1 is a gene associated with stem cells, which are involved in the self-renewal of blood and nervous stem cells as well as in tumorigenesis of different malignancies including leukemia, lymphoma, breast cancer, and lung cancer (8). Furthermore, recent studies reveal the relationship between CD133 and disease stage. This means that stage-3 tumors have more CD133 compared to stage-1 tumors (9). ALDH cells have a greater ability in developing spherical colonies, higher aggression capacity, and poorer response to chemotherapy (5,7).

As there is no review study about CSCs involved in the pathogenesis of OLP, for the first time we review the role of these cells in OLP and this hypothesis may be evidence for the evaluation of the premalignancy of OLP.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/sci-2020-049).

Methods

Search strategy

We have searched Medline (via PubMed and Ovid Medline) and Embase and Google scholar. The last search was done in July 2021 during the revision of the article. The search was done without any language limitation. Any kind of observational study was selected.

Our keywords were: [(oral lichen planus)] AND [(cancer stem cell) OR (ALDH) OR (CD44) OR (CD133) OR (C-Met) OR (side population cell)] and [(oral lichenoid reaction)] AND [(cancer stem cell) OR (ALDH) OR (CD44) OR (CD133) OR (CD24) OR (side population cell)].

To measure the risk of bias of the studies, the following criteria were considered: (I) age matching in the case and control groups; (II) gender matching in the case and control groups; (III) biopsy and considering WHO criteria to confirm Lichen Planus; (IV) matching in tobacco and alcohol use in the case and control groups. Alternatively, the lack of significant difference between the case and control groups in terms of consumption of these two points; (V) absence of history of malignancy and other autoimmune diseases in the control and case groups.

Risk of bias

(I) No risk: all points have been considered;
(II) Low risk: one point hasn't been considered;
(III) Intermediate risk: two-point haven't been considered;
(IV) High risk: three or more points haven't been considering.

Results

In the searches performed in the search engines mentioned above, 35 papers were found, whose full text was studied.

Table 1 Classification of the review papers according to inclusion and exclusion criteria

High risk	Intermediate risk	No risk and low risk
Rahmi Amtha, 2015 (10) (I, II, IV, V)	Andrea Santarelli, 2015 (11) (V, III)	Massoumeh Zargaran, 2018 (12) (IV)
Maria Siponen, 2015 (13) (I, II, V)	Ponlatham Chaiyarit, 2008 (14) (I, II)	Arash Mansourian, 2017 (15)
Narges Ghazi, 2020 (16) (II, III, IV, V)	Kaplan, 2015 (17) (V, IV)	Lili Sun, 2013 (18) (V)
	E. Neppelberg, 2007 (19) (V, IV)	Ziyuan Xu, 2013 (20) (V)
		Gui-Xiang Liu, 2011 (8) (I, II)

Table 2 CSCs in OLP

Article	Year	Cancer stem cell	Result	Media
M. Zargaran (12)	2018	CD44	Decrease	Tissue
A. Mansourian (15)	2017	ALDH	Increase	Saliva
GX. Liu (8)	2011	CD44	Increase	Plasma
M. Siponen (13)	2015	CD44	Increase	Tissue
Z. Xu (20)	2013	ALDH	Increase	Tissue
E. Nepplelberg (19)	2007	CD44	Decrease	Tissue
P. Chaiyarit (14)	2008	CD44	Increase and decrease	Tissue and saliva
A. Santralli (11)	2015	CD44	Increase	Tissue
L. Sun (18)	2013	CD133	Increase	Tissue
R. Amtha (10)	2015	CD133	Increase	Plasma
I. Kaplan (17)	2015	CD24	Increase	–
N. Ghazi (16)	2020	CD44	Increase	Tissue

CSCs, cancer stem cells; OLP, oral lichen planus.

Table 3 Comparison of CSCs in OLP and SCC

Stem cell	OLP	SCC
ALDH	Increase	Increase
CD44	Decrease and increase	Decrease and increase
CD133	Increase	Increase
CD24	Increase	Increase

CSCs, cancer stem cells; OLP, oral lichen planus; SCC, squamous cell carcinoma.

Meanwhile, 12 papers were related to this subject, which was assessed in terms of risk of bias criteria. Five papers had low risk or were risk-free, whereas other papers were grouped as intermediate or high-risk articles (*Table 1*).

Based on the related papers, two were related to ALDH, seven to CD44, two to CD133, and one to CD24. The two papers which dealt with ALDH indicated an elevation of this CSC in patients suffering from Lichen Planus, compared to the control. The article related to CD133 showed elevation of this CSC in the patients with Lichen Planus. The only study that measured CD24 levels in Lichen Planus patients indicated an elevation of this CSC among these people. The seven papers which were performed on CD44 indicated contradictory results, which was due to the measurement method of this CSC (*Table 2*). The comparison of CSCs in OLP and SCC is shown in *Table 3*.

Since there was only one paper available in the no or low-risk group about each marker, conducting meta-analysis in this review study was not possible.

Discussion

Evidence indicates that initiation, progress, relapse, and

metastases of head and neck cancer are related to a small subset of CSCs. Clinical and therapeutic documents about CSCs have shown the role of these markers in the early detection and prognosis of this cancer (5,7).

CSC term was coined by the American Association for Cancer as a cell capable of renewing itself and producing a group of cancer cells which include tumors. The major characteristics of CSCs which differentiate them from other cells include:

(I) Tumor induction if they are introduced into immunosuppressed mice;
(II) They have superficial markers, which are not expressed in other cells;
(III) The tumors that originate from CSCs have tumorigenic and non-tumorigenic cells;
(IV) They have self-renewal abilities and multipotency.

These properties originate from the internal characteristics of CSCs, which can create a second version, differentiate, and control the homeostasis. This subset of cells has been detected in several solid tumors including head and neck cancers and has special characteristics including metastasis and resistance to chemotherapy (7).

A recent study about CSCs in head and neck SCCs was showed that ALDH1A1 expression significantly higher in head and neck SCC *vs.* dysplasia, and CD133 expression levels were significantly higher in cancer and dysplasia patients *vs.* controls (21).

OLP may continue for several years, and there are periods of remission and aggravation with changes in its size and form. OLP may improve with treatment, but spontaneous improvement is uncommon. Oral lesions that have the most stable symptoms may be observed either alone or in combination with genital and dermal lesions (2).

The malignancy mechanism of OLP is still unknown. Erosive, atrophic, and ulcerative types having greater malignancy potential (1,2).

Among all of the studies reviewed in this article, all markers had increased expression in OLP compared to controls that are consistent with SCC. Meanwhile, only CD44 was in contradiction to other papers, in which different expression of CD44 strains was measured in different samples such as saliva and tissue.

CD44 is a molecule that attaches to the cell surface, which has a molecular weight of 80–250 kDalton. They exist in different cells including leukocytes, fibroblasts, endothelial cells, and epithelial cells (14,22). CD44 has various isoforms, whose most common isoform, also known as hematopoietic isoforms (7). CD44 is the main receptor for hyaluronic and has a tendency to other matrix components including fibronectin, collagen, osteopontin, and cytokines (13). Among the reviewed studies, CD44v6 indicated diminished expression in the tissue sample, while in the saliva sample of the affected individuals and normal people, there was no considerable difference. Meanwhile, CD44s and CD44v5 showed increased expression in the saliva samples and equal expression levels in the saliva of normal and patient individuals (14,22). It has been suggested that pathological stress including chronic OLP inflammation causes overregulation of proteolytic breakdown of several isoforms including CD44s and CD44v5, resulting in the liberation of these CD44 isoforms into saliva. This breakdown by enzymes including matrix metalloproteinase (MMP) has an important role in clearing CD44 off the cell surface (14). Also, recent studies indicate increased expression of MPPs in OLP which is correlated with malignancy potential in OLP (23). According to recent studies, it has been suggested that increased MMP expression in the tissue affected by Lichen Planus may result in the proteolytic breakdown of CD44s and CD44v5 off the surface of epithelial cells (14). Another mechanism stated for increased CD44 expression in the blood is the elevation of osteopontin in patients with lichen planus, which this increase causing abnormal migration of T-cell lymphocytes through increased expression of CD44 in OLP patients (13). This marker along with its ligand, hyaluronan is involved in various inflammatory diseases, including OLP. Investigating the role and functional mechanism of CD44 can serve as a therapeutic goal in chronic inflammatory diseases (16). Previous studies have shown that increased CD44 is associated with a worse outcome including metastasis and relapse in the colon, gastric, breast, and osteosarcoma cancers (7). Therefore, it could be concluded that in some types of OLP, with increased expression of this marker, conversion to malignancy, and the patient prognosis may be worse. Saghravanian *et al.* examined the extent of expression of CD44 and p53 in 45 patients with oral SCC and observed that the levels of both had a relationship with the stage of the disease. The more advanced the stage of the disease, the higher their level will be (24). The results of this study were consistent with the findings of other investigations. Recent studies suggest that the differential expression of CD44 is likely to depend on the location of lesions. This may be reliable for OLP as well (21).

Aldehyde hydrogenase family, with ALDH being one of them is a member of cytolytic isoenzymes, widely expressed in many stems and progenitors (7). Their

function involves the conversion of retinol to retinoic acid in the initial differentiation of stem cells and catalyzing the reaction of conversion of aldehyde metabolites to a carboxylic acid (20). ALDH expression has a direct relationship with the stage of head and neck cancer, and has a negative relationship with this is the prognosis. This biomarker plays a significant role in the metabolism of many molecules, causing detoxification of internal and external substances including alcohol and toxins (15). Oxidative stress results in carcinogenesis, which occurs due to an imbalance between the production of reactive oxygen species and the production of nitrogen species and antioxidant protective system. Recent theory has shown that signals that are produced due to chronic stimulations of inflammatory and stromal cells cause uncontrolled growth of epithelial cells along with oxidative stresses (1,2,15). These stresses lead to the production of oxidative and nitrative products, causing DNA damage, eventually bringing about neoplastic changes (15). Lipid peroxidation produces regenerated oxygen, causing the development of aldehyde. ALDH is responsible for removing aldehydes. Therefore, a high level of ALDH in the saliva of people with Lichen Planus is a defense mechanism against higher oxidative stress in these individuals (15). The expression profile of ALDH has been studied as putative CSC markers in oral SCC and cell lines (25). Zou *et al.* indicated a significant extent of ALDH expression in people with squamous cell tongue carcinoma (26).

CD133 is a transmembrane glycoprotein, which contains 865 amino acids with a molecular weight of 120 kDalton (10). CD133 function is unknown, but it increases in alteration processes including biological stress. For this reason, it is involved in tissue regeneration, inflammation, and the development of tumors (27). Studies have indicated that this biomarker circulates in the peripheral blood circulation, and when a tissue stimulation occurs or if it experiences tissue proliferation, it increases. EGFR is a tyrosine-kinase receptor, whose main function involves differentiation, proliferation, and migration. EGFR activity can cause the initiation and evolution of the tumor. It can also serve as a predictive marker in different cancers. Interestingly, it is in interaction with src-CD133. Some regions of tyrosine-kinase in EGFR are phosphorylated by src through physical contact (28). Previous studies showed that increased expression of CD133 is in association with the progress of pancreatic cancer, which occurs through activation of AKT which is dependent on EGFR. These effects involve EGFR-AKT signaling through direct interference between CD133 and EDFR. Resistance to drugs that target EGFR in clinical trials is possibly due to non-ligand-dependent activation of EGFR through interference with CD133. Further, recent studies have shown that overexpression of EGFR helps in carcinogenesis (28). Zou *et al.* revealed that EGFR has greater expression in erosive and ulcerative types, compared to other types (26). Zhang *et al.* showed that CD133 is abundantly found in the tissue prepared from OSCC patients. They also showed that CD133 cells have higher aggression potentials (29).

CD24 is a myosin adhesive molecule, which is expressed by pre-lymphocytes and neutrophils (17). Generally, CD24 propels metastasis and is known as a P-selectin ligand. CD24 is an activated receptor, which is activated on the surface of endothelial cells and platelets. Todoroki and Ghuwalewala indicated that cytoplasmic expression of CD24 is associated with adenocarcinoma of the colon, stomach, and ovules (30,31). Although the complete role of CD24 in the pathogenesis of malignancy of Lichen Planus is not completely clear, it has been indicated that it occurs through cell adhesion, apoptosis, regulation proliferation, and survival of B cells as well as T cells (17).

Investigation of CSC levels can be possible across soluble, integral, and transmembrane levels. Among the limitations of these studies mentioned in this research is not investigating CSC across all of the three levels concurrently. For example, in the study by Siponen *et al.*, it has been shown that CD44v6 in saliva whose soluble form exists is different from immuno-histo-chemical results examining its tissue form (13). These findings suggest that regulation of expression of each CD44 isoform in the mucus and saliva may occur through different pathways.

Conclusions

In conclusion CSCs expression is increased in OLP as the same as oral SCC. This can reinforce the malignant potential of OLP especially with increasing CSCs levels in atrophic-erosive forms compare to reticular forms. Based on the results of this study, it is suggested that the expression of CSCs, which are known as a marker in epithelial-originated cancers be examined in OLP. This is because the malignancy potential of this disease is still unknown and perhaps in the future by investigating the levels of these markers in OLP, it may be possible to determine the prognosis and course of the disease for each patient individually. On the other hand,

as no definite treatment has been found for OLP, novel target therapy using CSCs may be a better treatment or complement the conventional treatments.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://dx.doi.org/10.21037/sci-2020-049

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/sci-2020-049). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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